WEST Search History

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DATE: Thursday, June 01, 2006

Hide?	Set Name	Query	Hit Count
		DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ	
☐	L9	cleav$5 same L8	6
☐	L8	(agent or modulat$5 or inhibit$5 or activat$5) same L2	8
☐	L7	(modulat$5 or inhibit$5 or activat$5) same L2	8
☐	L6	cleav$5 same L5	8
☐	L5	(agent or modulat$5 or inhibit$5 or activat$5) same L3	27
☐	L4	(modulat$5 or inhibit$5 or activat$5) same L3	25
☐	L3	(metalloprotease or BMP$3 or TLD$3 or TLL$3)same L1	34
☐	L2	metalloprotease same L1	8
☐	L1	(myostatin or promyostatin)	173

END OF SEARCH HISTORY

=> index bioscience medicine

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE, AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS, CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB, DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 16:30:09 ON 01 JUN 2006

71 FILES IN THE FILE LIST IN STNINDEX

=> S ((latent(w)myostatin)or myostatin or promyostatin)
2 FILE ADISINSIGHT
1 FILE ADISNEWS
60 FILE AGRICOLA
1 FILE ANABSTR
2 FILE ANTE
14 FILE AQUASCI
34 FILE BIOENG
426 FILE BIOSIS
44 FILE BIOTECHABS
44 FILE BIOTECHDS
106 FILE BIOTECHNO
192 FILE CABA
432 FILE CAPLUS
9 FILE CIN
21 FILE CONFSCI
3 FILE DDFB
12 FILE DDFU
2242 FILE DGENE
22 FILE DISSABS
3 FILE DRUGB
16 FILE DRUGU
13 FILE EMBAL
303 FILE EMBASE
29 FILES SEARCHED...
238 FILE ESBIOBASE
21 FILE FROSTI
17 FILE FSTA
344 FILE GENBANK
53 FILE IFIPAT
4 FILE IMSDRUGNEWS
3 FILE IMSRESEARCH
15 FILE JICST-EPLUS
91 FILE LIFESCI
312 FILE MEDLINE
1 FILE NTIS
1 FILE NUTRACEUT
46 FILES SEARCHED...
5 FILE OCEAN
99 FILE PASCAL
3 FILE PHAR
11 FILE PHIN
35 FILE PROMT
2 FILE PROUSDDR
472 FILE SCISEARCH
79 FILE TOXCENTER
123 FILE USPATFULL
4 FILE USPAT2
3 FILE VETU
65 FILES SEARCHED...
46 FILE WPIDS
3 FILE WPIFV
67 FILES SEARCHED...
46 FILE WPINDEX
24 FILE NLDB

50 FILES HAVE ONE OR MORE ANSWERS, 71 FILES SEARCHED IN STNINDEX

L1 QUE ((LATENT(W) MYOSTATIN) OR MYOSTATIN OR PROMYOSTATIN)

=> d rank

F1	2242	DGENE
F2	472	SCISEARCH
F3	432	CAPLUS
F4	426	BIOSIS
F5	344	GENBANK
F6	312	MEDLINE
F7	303	EMBASE
F8	238	ESBIOBASE
F9	192	CABA
F10	123	USPATFULL
F11	106	BIOTECHNO
F12	99	PASCAL
F13	91	LIFESCI
F14	79	TOXCENTER
F15	60	AGRICOLA
F16	53	IFIPAT
F17	46	WPIDS
F18	46	WPINDEX
F19	44	BIOTECHABS
F20	44	BIOTECHDS

=> file f2-f4, f6-f17

FILE 'SCISEARCH' ENTERED AT 16:33:54 ON 01 JUN 2006

FILE 'CAPLUS' ENTERED AT 16:33:54 ON 01 JUN 2006

FILE 'BIOSIS' ENTERED AT 16:33:54 ON 01 JUN 2006

FILE 'MEDLINE' ENTERED AT 16:33:54 ON 01 JUN 2006

FILE 'EMBASE' ENTERED AT 16:33:54 ON 01 JUN 2006

FILE 'ESBIOBASE' ENTERED AT 16:33:54 ON 01 JUN 2006

FILE 'CABA' ENTERED AT 16:33:54 ON 01 JUN 2006

FILE 'USPATFULL' ENTERED AT 16:33:54 ON 01 JUN 2006

FILE 'BIOTECHNO' ENTERED AT 16:33:54 ON 01 JUN 2006

FILE 'PASCAL' ENTERED AT 16:33:54 ON 01 JUN 2006

FILE 'LIFESCI' ENTERED AT 16:33:54 ON 01 JUN 2006

FILE 'TOXCENTER' ENTERED AT 16:33:54 ON 01 JUN 2006

FILE 'AGRICOLA' ENTERED AT 16:33:54 ON 01 JUN 2006

FILE 'IFIPAT' ENTERED AT 16:33:54 ON 01 JUN 2006

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FILE 'WPIDS' ENTERED AT 16:33:54 ON 01 JUN 2006
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=> s L1
L2 3032 L1

=> s (metalloprotease or BMP? or TLD? or TLL?)(s)L2
L3 119 (METALLOPROTEASE OR BMP? OR TLD? OR TLL?)(S) L2

=> s (agent or modulat? or inhibit? or activat?)(s)L3
7 FILES SEARCHED...
11 FILES SEARCHED...
L4 63 (AGENT OR MODULAT? OR INHIBIT? OR ACTIVAT?)(S) L3

=> s cleav?(s)L4
L5 23 CLEAV?(S) L4

=> dup rem L5
PROCESSING COMPLETED FOR L5
L6 13 DUP REM L5 (10 DUPLICATES REMOVED)

=> d ibib abs L6 1-13

L6 ANSWER 1 OF 13 USPATFULL on STN
ACCESSION NUMBER: 2006:9997 USPATFULL
TITLE: Antagonism of TGF-beta superfamily receptor signaling
INVENTOR(S): Vale, Wylie, La Jolla, CA, UNITED STATES
Harrison, Craig, Nunawading, AUSTRALIA
Gray, Peter, San Diego, CA, UNITED STATES
Fischer, Wolfgang, Encinitas, CA, UNITED STATES
Choe, Senyon, Solana Beach, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2006008846	A1	20060112
APPLICATION INFO.:	US 2005-115877	A1	20050427 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2004-565594P	20040427 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FULBRIGHT & JAWORSKI, LLP, 1301 MCKINNEY, SUITE 5100, HOUSTON, TX, 77010-3095, US
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Page(s)
LINE COUNT: 1872
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Members of the TGF-.beta. superfamily control many physiologic and pathophysiologic processes in multiple tissues and signal via type II and type I receptor serine kinases. Type II activin receptors are promiscuous and known to bind 12 TGF-.beta. ligands including activins, myostatin, BMPs and nodal. Methods are described for the screening and identification of antagonist for TGF-.beta. superfamily members, in particular activin-A antagonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2006:474546 CAPLUS
TITLE: Developmental roles of the BMP1/TLD metalloproteinases
AUTHOR(S): Ge, Gaoxiang; Greenspan, Daniel S.
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI, USA
SOURCE: Birth Defects Research, Part C: Embryo Today--Reviews (2006), 78(1), 47-68
CODEN: BDRPDV; ISSN: 1542-975X

PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The astacin family (M12A) of the metzincin subclan MA(M) of metalloproteinases has been detected in developing and mature individuals of species that range from hydra to humans. Functions of this family of metalloproteinase vary from digestive degrdn. of polypeptides, to biosynthetic processing of extracellular proteins, to activation of growth factors. This review will focus on a small subgroup of the astacin family; the bone morphogenetic protein 1 (BMP1)/Tolloid (TLD)-like metalloproteinases. In vertebrates, the BMP1/TLD-like metalloproteinases play key roles in regulating formation of the extracellular matrix (ECM) via biosynthetic processing of various precursor proteins into mature functional enzymes, structural proteins, and proteins involved in initiating mineralization of the ECM of hard tissues. Roles in ECM formation include: processing of the C-propeptides of procollagens types I-III, to yield the major fibrous components of vertebrate ECM; proteolytic activation of the enzyme lysyl oxidase, necessary to formation of covalent cross-links in collagen and elastic fibers; processing of NH2-terminal globular domains and C-propeptides of types V and XI procollagen chains to yield monomers that are incorporated into and control the diams. of collagen type I and II fibrils, resp.; processing of precursors for laminin 5 and collagen type VII, both of which are involved in securing epidermis to underlying dermis; and maturation of small leucine-rich proteoglycans. The BMP1/TLD-related metalloproteinases are also capable of activating the vertebrate transforming growth factor-.beta. (TGF-.beta.)-like "chalones" growth differentiation factor 8 (GDF8, also known as myostatin), and GDF11 (also known as BMP11), involved in neg. feedback inhibition of muscle and neural tissue growth, resp.; by freeing them from noncovalent latent complexes with their cleaved prodomains. BMP1/TLD-like proteinases also liberate the vertebrate TGF-.beta.-like morphogens BMP2 and 4 and their invertebrate ortholog decapentaplegic, from latent complexes with the vertebrate extracellular antagonist chordin and its invertebrate ortholog short gastrulation (SOG), resp. The result is formation of the BMP signaling gradients that form the dorsal-ventral axis in embryogenesis. Thus, BMP1/TLD-like proteinases appear to be key to regulating and orchestrating formation of the ECM and signaling by various TGF-.beta.-like proteins in morphogenetic and homeostatic events.
REFERENCE COUNT: 229 THERE ARE 229 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 13 USPATFULL on STN DUPLICATE 2
ACCESSION NUMBER: 2005:50433 USPATFULL
TITLE: Metalloprotease activation of myostatin, and methods of modulating myostatin activity
INVENTOR(S): Lee, Se-Jin, Baltimore, MD, UNITED STATES
McPherron, Alexandra C., Baltimore, MD, UNITED STATES
Greenspan, Daniel S., Madison, WI, UNITED STATES
Pappano, William N., Columbia, MD, UNITED STATES
Wolfman, Neil, Dover, MA, UNITED STATES
Tomkinson, Kathy, Cambridge, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2005043232	A1	20050224
APPLICATION INFO.:	US 2003-665374	A1	20030916 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-486863P	20030710 (60)
	US 2003-439164P	20030109 (60)
	US 2002-411133P	20020916 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: GRAY CARY WARE & FREIDENRICH LLP, 4365 EXECUTIVE DRIVE, SUITE 1100, SAN DIEGO, CA, 92121-2133
NUMBER OF CLAIMS: 66

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Page(s)
LINE COUNT: 2732
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB It has been determined that metalloprotease cleavage of a myostatin pro peptide results in activation of a latent inactive myostatin to an active form. Accordingly, methods of identifying agents that modulate metalloprotease mediated activation of myostatin are provided, as are agents identified using such methods. Also provided are methods of modulating muscle growth in an organism by increasing or decreasing metalloprotease mediated cleavage of a myostatin pro peptide.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 4 OF 13 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
ACCESSION NUMBER: 2005-285404 [29] WPIDS
DOC. NO. CPI: C2005-088616
TITLE: New muscle-targeting fusion protein for treating muscle-related diseases, e.g. muscle atrophy, comprises a ligand that binds a target surface protein; a therapeutic agent; and a multimerizing component and/or a signal sequence.
DERWENT CLASS: B04 D16
INVENTOR(S): GLASS, D J
PATENT ASSIGNEE(S): (GLAS-I) GLASS D J; (REGE-N) REGENERON PHARM INC
COUNTRY COUNT: 108
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005033134	A2	20050414 (200529)*		EN	84

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

US 2005287151 A1 20051229 (200603)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005033134	A2	WO 2004-US32233	20040930
US 2005287151	A1 Provisional	US 2003-507168P	20030930
	Provisional	US 2003-516806P	20031103
	Provisional	US 2003-529826P	20031216
	Provisional	US 2004-534654P	20040107
	Provisional	US 2004-534819P	20040107
	Provisional	US 2004-554640P	20040319
	Provisional	US 2004-573525P	20040521
	Provisional	US 2004-581833P	20040622
	Provisional	US 2004-584956P	20040702
		US 2004-954468	20040930

PRIORITY APPLN. INFO: US 2004-584956P 20040702; US 2003-507168P 20030930; US 2003-516806P 20031103; US 2003-529826P 20031216; US 2004-534654P 20040107; US 2004-534819P 20040107; US 2004-554640P 20040319; US 2004-573525P 20040521; US 2004-581833P 20040622; US 2004-954468 20040930
AN 2005-285404 [29] WPIDS

AB WO2005033134 A UPAB: 20050506
NOVELTY - A targeting fusion polypeptide comprising a first component comprising a targeting ligand, or its derivative or fragment, capable of binding specifically to a pre-selected cell surface protein; a second component comprising at least one active or therapeutic agent; and optionally, a multimerizing component capable of forming a multimer with another targeting fusion polypeptide; and/or a signal sequence, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) an isolated nucleic acid molecule encoding the above fusion polypeptide; and
(2) a pharmaceutical composition comprising the above fusion polypeptide and a carrier.
ACTIVITY - Muscular-Gen. No biological data given.
MECHANISM OF ACTION - Gene therapy.
USE - The fusion protein is useful in therapy or in the manufacture of a medicament for the treatment of a muscle-related condition or disease in a subject suffering from a condition which would benefit from the medicament, such as muscle atrophy or muscle dystrophy (claimed).
Dwg.0/0

L6 ANSWER 5 OF 13 Elsevier BIOBASE COPYRIGHT 2006 Elsevier Science B.V. on STN
ACCESSION NUMBER: 2005179489 ESBIOBASE
TITLE: GDF11 forms a bone morphogenetic protein 1-activated latent complex that can modulate nerve growth factor-induced differentiation of PC12 cells
AUTHOR: Ge G.; Hopkins D.R.; Ho W.-B.; Greenspan D.S.
CORPORATE SOURCE: D.S. Greenspan, Department of Pathology and Laboratory Medicine, University of Wisconsin, 1300 University Avenue, Madison, WI 53706, United States.
E-mail: dsgreens@wisc.edu
SOURCE: Molecular and Cellular Biology, (2005), 25/14 (5846-5858), 45 reference(s)
CODEN: MCEBD4 ISSN: 0270-7306
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AB All transforming growth factor .beta. (TGF-.beta.) superfamily members are synthesized as precursors with prodomain sequences that are proteolytically removed by subtilisin-like proprotein convertases (SPCs). For most superfamily members, this is believed sufficient for activation. Exceptions are TGF-.beta.s 1 to 3 and growth differentiation factor 8 (GDF8), also known as myostatin, which form noncovalent, latent complexes with their SPC-cleaved prodomains. Sequence similarities between TGF-.beta.s 1 to 3, myostatin, and superfamily member GDF11, also known as bone morphogenetic protein 11 (BMP11), prompted us to examine whether GDF11 might be capable of forming a latent complex with its cleaved prodomain. Here we demonstrate that GDF11 forms a noncovalent latent complex with its SPC-cleaved prodomain and that this latent complex is activated via cleavage at a single specific site by members of the developmentally important BMP1/Tolloid family of metalloproteinases. Evidence is provided for a molecular model whereby formation and activation of this complex may play a general role in modulating neural differentiation. In particular, mutant GDF11 prodomains impervious to cleavage by BMP1/Tolloid proteinases are shown to be potent stimulators of neurodifferentiation, with potential for therapeutic applications. Copyright .COPYRGT. 2005, American Society for Microbiology. All Rights Reserved.

L6 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2004:252617 CAPLUS
DOCUMENT NUMBER: 140:249207
TITLE: Modulating myostatin activity with metalloprotease and use in controlling muscle growth
INVENTOR(S): Lee, Se-jin; Mcpherron, Alexandra C.; Greenspan, Daniel S.; Pappano, William N.; Wolfman, Neil; Tomkinson, Kathy

PATENT ASSIGNEE(S): The Johns Hopkins University, USA; Wisconsin Alumni Research Foundation; Wyeth, John, and Brother Ltd.
SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004024890	A2	20040325	WO 2003-US29079	20030916
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2496213	AA	20040325	CA 2003-2496213	20030916
AU 2003267246	A1	20040430	AU 2003-267246	20030916
US 2004138118	A1	20040715	US 2003-662438	20030916
US 2005043232	A1	20050224	US 2003-665374	20030916
BR 2003014270	A	20050802	BR 2003-14270	20030916
EP 1578928	A2	20050928	EP 2003-749716	20030916
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
CN 1694957	A	20051109	CN 2003-825168	20030916

PRIORITY APPLN. INFO.: US 2002-411133P P 20020916
US 2003-439164P P 20030109
US 2003-486863P P 20030710
WO 2003-US29079 W 20030916

AB It has been detd. that metalloprotease cleavage of a myostatin pro peptide results in activation of a latent inactive myostatin to an active form. Accordingly, methods of identifying agents that modulate metalloprotease mediated activation of myostatin are provided, as are agents identified using such methods. Also provided are methods of modulating muscle growth in an organism by increasing or decreasing metalloprotease mediated cleavage of a myostatin pro peptide.

L6 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2006 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2004:252308 CAPLUS
DOCUMENT NUMBER: 140:283388
TITLE: Modulating myostatin activity with metalloprotease and use in controlling muscle mass and treating muscle wasting disorder
INVENTOR(S): Wolfman, Neil; Tomkinson, Kathy
PATENT ASSIGNEE(S): Wyeth, John, and Brother Ltd., USA
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004024092	A2	20040325	WO 2003-US28907	20030916
WO 2004024092	A3	20040826		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,				

KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
CA 2498044 AA 20040325 CA 2003-2498044 20030916
AU 2003272394 A1 20040430 AU 2003-272394 20030916
US 2004138118 A1 20040715 US 2003-662438 20030916
US 2005043232 A1 20050224 US 2003-665374 20030916
EP 1549747 A2 20050706 EP 2003-754574 20030916
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
BR 2003014380 A 20050719 BR 2003-14380 20030916
CN 1694957 A 20051109 CN 2003-825168 20030916
JP 2006507356 T2 20060302 JP 2004-572009 20030916
PRIORITY APPLN. INFO.: US 2002-411133P P 20020916
US 2003-439164P P 20030109
US 2003-486863P P 20030710
WO 2003-US28907 W 20030916
AB It has been detd. that metalloprotease cleavage of a myostatin pro peptide results in activation of a latent inactive myostatin to an active form. Accordingly, methods of identifying agents that modulate metalloprotease mediated activation of myostatin are provided, as are agents identified using such methods. Also provided are methods of modulating muscle growth in an organism by increasing or decreasing metalloprotease mediated cleavage of a myostatin pro peptide. The invention demonstrated that cleavage of the pro peptides by BMP-1/ tolloid (TLD) proteinase. The invention further relates to treating muscle wasting disease assocd. with muscular dystrophy, cachexia, sarcopenia, diabetes and obesity.

L6 ANSWER 8 OF 13 USPATFULL on STN DUPLICATE 5
ACCESSION NUMBER: 2004:178948 USPATFULL
TITLE: Metalloprotease activation of myostatin, and methods of modulating myostatin activity
INVENTOR(S): Wolfman, Neil, Dover, MA, UNITED STATES
Tomkinson, Kathy, Cambridge, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004138118	A1	20040715
APPLICATION INFO.:	US 2003-662438	A1	20030916 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-486863P	20030710 (60)
	US 2003-439164P	20030109 (60)
	US 2002-411133P	20020916 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FINNEGAN, HENDERSON, FARABOW,, GARRETT & DUNNER, L.L.P., 1300 I Street, N.W., Washington, DC, 20005
NUMBER OF CLAIMS: 21
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Page(s)
LINE COUNT: 2598
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB It has been determined that metalloprotease cleavage of a myostatin pro peptide results in activation of a latent inactive myostatin to an active form. Accordingly, methods of identifying agents that modulate metalloprotease mediated activation of myostatin are provided, as are agents identified using such methods. Also provided are methods of modulating muscle growth in an organism by increasing or decreasing metalloprotease mediated cleavage of a myostatin pro peptide.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 9 OF 13 USPATFULL on STN
ACCESSION NUMBER: 2004:39572 USPATFULL

TITLE: Myostatin regulatory region, nucleotide sequence determination and methods for its use
INVENTOR(S): Findly, Robert Craig, Wethersfield, CT, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004030114	A1	20040212
APPLICATION INFO.:	US 2003-610473	A1	20030630 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 2000-626959, filed on 27 Jul 2000, GRANTED, Pat. No. US 6617440

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-146540P	19990730 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KOHN & ASSOCIATES, PLLC, Suite 410, 30500 Northwestern Highway, Farmington Hills, MI, 48334
NUMBER OF CLAIMS: 28
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 1123
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a transcription regulatory region of a myostatin gene. In particular, the invention relates to a 2.5 kb polynucleotide immediately 5' to the myostatin coding sequence, its nucleotide sequence and methods of using this regulatory region, and fragments thereof. The present invention relates to the use of the myostatin promoter of the present invention to direct expression of a target gene in a tissue specific manner, i.e. muscle tissue. The present invention relates to the use of the myostatin promoter of the present invention in high throughput screens to identify test compounds which inhibit myostatin promoter activity or myostatin expression. In accordance with the present invention, inhibitors of the myostatin promoter may be used to inhibit myostatin expression as a method of engineering animals with increased lean meat in order to decrease the time required to bring the animals to slaughter, and of promoting muscle growth for treating disorders related to expression of the myostatin gene, such as muscle wasting associated with aging or disease in humans and companion animals, particularly cats and dogs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 10 OF 13 USPATFULL on STN
ACCESSION NUMBER: 2003:240451 USPATFULL
TITLE: Myostatin regulatory region, nucleotide sequence determination and methods for its use
INVENTOR(S): Findly, Robert Craig, Wethersfield, CT, United States
PATENT ASSIGNEE(S): Pfizer, Inc., New York, NY, United States (U.S. corporation)
Pfizer Products, Inc., Groton, CT, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6617440	B1	20030909
APPLICATION INFO.:	US 2000-626959		20000727 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-146540P	19990730 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Wehbe', Anne M.
ASSISTANT EXAMINER: Li, Q Janice
LEGAL REPRESENTATIVE: Ginsburg, Paul H., Ling, Lorraine B., Kohn & Associates, PLLC
NUMBER OF CLAIMS: 6
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Figure(s); 4 Drawing Page(s)

LINE COUNT: 1016
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a transcription regulatory region of a myostatin gene. In particular, the invention relates to a 2.5 kb polynucleotide immediately 5' to the myostatin coding sequence, its nucleotide sequence and methods of using this regulatory region, and fragments thereof. The present invention relates to the use of the myostatin promoter of the present invention to direct expression of a target gene in a tissue specific manner, i.e. muscle tissue. The present invention relates to the use of the myostatin promoter of the present invention in high throughput screens to identify test compounds which inhibit myostatin promoter activity or myostatin expression. In accordance with the present invention, inhibitors of the myostatin promoter may be used to inhibit myostatin expression as a method of engineering animals with increased lean meat in order to decrease the time required to bring the animals to slaughter, and of promoting muscle growth for treating disorders related to expression of the myostatin gene, such as muscle wasting associated with aging or disease in humans and companion animals, particularly cats and dogs.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L6 ANSWER 11 OF 13 IFIPAT COPYRIGHT 2006 IFI on STN
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TITLE: FOLLISTATIN DOMAIN CONTAINING PROTEINS; CONTROLLING CELL DIFFERENTIATION; MUSCULAR DISORDERS
INVENTOR(S): Hill; Jennifer J., Somerville, MA, US
Wolfman; Neil M., Dover, MA, US
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	NUMBER	PK	DATE
PATENT INFORMATION:	US 2003180306	A1	20030925
APPLICATION INFORMATION:	US 2003-369738		20030221

	NUMBER	DATE
PRIORITY APPLN. INFO.:	US 2002-357846P	20020221 (Provisional)
	US 2002-434645P	20021220 (Provisional)

FAMILY INFORMATION: US 2003180306 20030925
DOCUMENT TYPE: Utility
Patent Application - First Publication
FILE SEGMENT: CHEMICAL
APPLICATION

PARENT CASE DATA:

This application claims the benefit of U.S. Provisional Application No. 60/357,846, filed Feb. 21, 2002, and U.S. Provisional Application No. 60/434,645, filed Dec. 20, 2002.

NUMBER OF CLAIMS: 47 18 Figure(s).
DESCRIPTION OF FIGURES:
FIG. 1 shows antibody purification of the GDF-8 complex from wild-type mouse serum. A silver stained reducing gel shows proteins purified from wild type mouse serum using the JA16 monoclonal antibody covalently coupled to agarose beads. A control purification (0) with mock-coupled beads was performed in parallel. Subsequent elutions with buffer (mock elute), a competing peptide, and SDS sample buffer revealed two visible protein bands which were specifically eluted with peptide from the JA16-conjugated beads (indicated by arrows).
FIG. 2 shows the identification of mature and unprocessed GDF-8 in affinity purified samples from normal mouse serum. FIG. 2A shows a representative MS/MS spectrum of a GDF-8 derived peptide (SEQ ID NO:19) identified from the 12 kDa band visible in the affinity purified sample. Both N-terminal fragment ions (b ions) and C-terminal fragment ions (y ions) are visible. Notably, the most intense y fragment ions result from fragmentation before the proline residue, a

common characteristic of proline containing peptides. FIG. 2B shows a western blot probed with a polyclonal antibody that recognizes the mature region of GDF-8, confirming the presence of GDF-8 in the affinity purified samples. Both the mature and unprocessed forms of GDF-8 are visible.

FIG. 3 shows the GDF-8 propeptide and follistatin-like related gene (FLRG) bind to circulating GDF-8 isolated from normal mouse serum. Representative MS/MS spectra from GDF-8 propeptide (SEQ ID NO:23) (FIG. 3A) and FLRG (SEQ ID NO:30) (FIG. 3C) derived peptides identified in the 36 kDa band are shown. FIG. 3B shows a western blot of affinity purified GDF-8 complex probed with a polyclonal antibody that specifically recognizes the propeptide region of GDF-8, confirming the mass spectrometric identification of this protein in the GDF-8 complex. Both the clipped propeptide and unprocessed GDF-8 are visible-at longer exposures, unprocessed GDF-8 can also be seen in the SDS eluted sample. FIG. 3D shows a western blot of affinity purified GDF-8 complex probed with a monoclonal antibody to FLRG.

FIG. 4 shows results from a thorough analysis of a large scale GDF-8 purification that identified GDF-8 propeptide, FLRG, and a novel protein as the major GDF-8 binding proteins in serum. A silver stained gel was dissected into 13 slices from the peptide eluted sample of both negative control and JA16 immunoprecipitates. The proteins in each slice were digested with trypsin and identified using nanoflow-LC-MS/MS and database searching. Proteins unique to the JA16 sample included only unprocessed and mature GDF-8, GDF-8 propeptide, FLRG, and a novel multidomain protease inhibitor (GDF-associated serum protein 1, GASP1). These proteins were identified from the noted regions of the gel.

FIG. 5 shows that a novel multidomain protease inhibitor, GASP1, is bound to GDF-8 in serum. FIGS. 5A (peptide assigned SEQ ID NO:31) and 5B (peptide assigned SEQ ID NO:33) show representative MS/MS spectra from two GASP1 peptides, identified in band 3 of the silver stained gel of FIG. 4.

FIG. 6A shows the predicted nucleotide sequence to mouse GASP1.

FIG. 6B shows a predicted alternative nucleotide sequence to mouse GASP1. FIG. 6C shows the predicted amino acid sequence encoded by the nucleotide sequences shown in FIGS. 6A and 6B. The protein sequences encoded by the two nucleotide sequences are identical because the nucleotide differences are all in wobble codon positions. The follistatin domain is shown in bold and underlined.

FIG. 7A shows the predicted nucleotide sequence of human GASP1. FIG. 7B shows the corresponding predicted amino acid sequence. The follistatin domain is shown in bold and underlined. FIG. 7C shows the predicted nucleotide sequence of human GASP1 using an alternative start site. FIG. 7D shows the corresponding predicted amino acid sequence. The follistatin domain is shown in bold and underlined. The end of the sequence is denoted by the asterisk.

FIG. 8A shows the predicted nucleotide sequence to mouse GASP2, while FIG. 8B shows the corresponding predicted amino acid sequence. The follistatin domain is shown in bold and underlined.

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FIG. 12 shows representative mass spectra of a peptide derived from GDF-8 and associated proteins isolated from bands 4, 11, and 16 (FIG. 11). The peptide sequence and N-terminal (b ions) and C-terminal (y ions) are shown. A complete listing of identified peptides is provided in Table 1. Spectra are shown from a GASP1 peptide (SEQ ID NO:44) (FIG. 12A), a FLRG peptide (SEQ ID NO:41) (FIG.

12B), a GDF-8 propeptide peptide (SEQ ID NO:24) (FIG. 12C), and a mature GDF-8 peptide (SEQ ID NO:13) (FIG. 12D).
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FIG. 14A shows the domain structure of GASP1. GASP1 has a signal sequence/ ***cleavage*** site after amino acid 29. In addition, GASP1 contains two Kunitz/BPTI serine protease inhibitor domains, a follistatin domain (including a Kazal serine protease inhibitor motif) and a netrin domain, which may inhibit metalloproteases. FIG. 14B shows the phylogenetic tree of GASP1 and GASP2 predicted from the mouse and human genomic sequences. Mouse and human GASP1 are 90% identical. GASP1 and GASP2 are 54% identical.
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FIG. 16 shows that GASP1 inhibits the biological activity of GDF8 and the highly related BMP-11, but not activin or TGF-beta . Various dilutions of conditioned media from mock (open circles) or GASP1-V5-His (filled squares) transfectants were incubated with (A) 10 ng/ml GDF-8, (B) 10 ng/ml ***BMP*** -11, (C) 10 ng/ml activin, or (D) 0.5 ng/ml TGF-beta . These samples were then subjected to a luciferase reporter activity assay in A204 (A-C) or RD (D) cells to determine the activity of the added growth factors. Luciferase activity is shown in relative luciferase units. The activity resulting from each of the growth factors alone is shown by the filled diamonds and short dashed line. Without addition of any growth factor, the background activity in the assay is low, as shown by the long dashed line with no symbols.
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AB The present invention relates to the use of proteins comprising at least one follistatin domain to modulate the level or activity of growth and differentiation factor-8 (GDF-8). More particularly, the invention relates to the use of proteins comprising at least one follistatin domain, excluding follistatin itself, for treating disorders that are related to modulation of the level or activity of GDF-8. The invention is useful for treating muscular diseases and disorders, particularly those in which an increase in muscle tissue would be therapeutically beneficial. The invention is also useful for treating diseases and disorders related to metabolism, adipose tissue, and bone degeneration.
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L6 ANSWER 12 OF 13 IFIPAT COPYRIGHT 2006 IFI on STN
AN 10418290 IFIPAT;IFIUDB;IFICDB
TITLE: GASP1: A FOLLISTATIN DOMAIN CONTAINING PROTEIN; MODULATE CELL DIFFERENTIATION; MUSCULAR DISORDERS; FAT METABOLISM; BONE DISORDERS
INVENTOR(S): Hill; Jennifer J., Somerville, MA, US
Wolfman; Neil M., Dover, MA, US
PATENT ASSIGNEE(S): WYETH, US
AGENT: Rebecca M. McNeill Finnegan, Henderson, Farabow,, Garrett & Dunner, L.L.P., 1300 I Street, N.W., Washington, DC, 20005-3315, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2003162714	A1	20030828
APPLICATION INFORMATION:	US 2003-369736		20030221

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PRIORITY APPLN. INFO.:	US 2002-357845P	20020221 (Provisional)
	US 2002-434644P	20021220 (Provisional)
FAMILY INFORMATION:	US 2003162714	20030828

DOCUMENT TYPE: Utility
Patent Application - First Publication

FILE SEGMENT: CHEMICAL
APPLICATION
OTHER SOURCE: CA 139:202590

PARENT CASE DATA:

This application claims the benefit of U.S. Provisional Application No. 60/357,845, filed Feb. 21, 2002, and U.S. Provisional Application No. 60/434,644, filed Dec. 20, 2002.

NUMBER OF CLAIMS: 47 17 Figure(s).

DESCRIPTION OF FIGURES:

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FIG. 1 shows antibody purification of the GDF-8 complex from wild-type mouse serum. A silver stained reducing gel shows proteins purified from wild type mouse serum using the JA16 monoclonal antibody covalently coupled to agarose beads. A control purification (0) with mock-coupled beads was performed in parallel. Subsequent elutions with buffer (mock elute), a competing peptide, and SDS sample buffer revealed two visible protein bands which were specifically eluted with peptide from the JA16-conjugated beads (indicated by arrows).

FIG. 2 shows the identification of mature and unprocessed GDF-8 in affinity purified samples from normal mouse serum. FIG. 2A shows a representative MS/MS spectrum of a GDF-8 derived peptide (SEQ ID NO:19) identified from the 12 kDa band visible in the affinity purified sample. Both N-terminal fragment ions (b ions) and C-terminal fragment ions (y ions) are visible. Notably, the most intense y fragment ions result from fragmentation before the proline residue, a common characteristic of proline containing peptides. FIG. 2B shows a western blot probed with a polyclonal antibody that recognizes the mature region of GDF-8, confirming the presence of GDF-8 in the affinity purified samples. Both the mature and unprocessed forms of GDF-8 are visible.

FIG. 3 shows the GDF-8 propeptide and follistatin-like related gene (FLRG) bind to circulating GDF-8 isolated from normal mouse serum. Representative MS/MS spectra from GDF-8 propeptide (SEQ ID NO:23) (FIG. 3A) and FLRG (SEQ ID NO:30) (FIG. 3C) derived peptides identified in the 36 kDa band are shown. FIG. 3B shows a western blot of affinity purified GDF-8 complex probed with a polyclonal antibody that specifically recognizes the propeptide region of GDF-8, confirming the mass spectrometric identification of this protein in the GDF-8 complex. Both the clipped propeptide and unprocessed GDF-8 are visible-at longer exposures, unprocessed can also be seen in the SDS eluted sample. FIG. 3D shows a western blot of affinity purified GDF-8 complex probed with a monoclonal antibody to FLRG.

FIG. 4 shows results from a thorough analysis of a large scale GDF-8 purification that identified GDF-8 propeptide, FLRG, and a novel protein as the major GDF-8 binding proteins in serum. A silver stained gel was dissected into 13 slices from the peptide eluted sample of both negative control and JA16 immunoprecipitates. The proteins in each slice were digested with trypsin and identified using nanoflow-LC-MS/MS and database searching. Proteins unique to the JA16 sample included only unprocessed and mature GDF-8, GDF-8 propeptide, FLRG, and a novel multidomain protease inhibitor (GDF-associated serum protein 1, GASP1). These proteins were identified from the noted regions of the gel.

FIG. 5 shows that a novel multidomain protease inhibitor, GASP1, is bound to GDF-8 in serum. FIGS. 5A (peptide assigned SEQ ID NO:31) and 5B (peptide assigned SEQ ID NO:33) show representative MS/MS spectra from two GASP1 peptides, identified in band 3 of the silver stained gel of FIG. 4.

FIG. 6A shows the predicted nucleotide sequence to mouse GASP1. FIG. 6B shows a predicted alternative nucleotide sequence to mouse GASP1. FIG. 6C shows the predicted amino acid sequence encoded by the nucleotide sequences shown in FIGS. 6A and 6B. The protein sequences encoded by the two nucleotide sequences are identical because the nucleotide differences are all in wobble codon positions. The follistatin domain is shown in bold and underlined.

FIG. 7A shows the predicted nucleotide sequence of human GASP1. FIG. 7B shows the corresponding predicted amino acid sequence. The follistatin domain is shown in bold and underlined. FIG. 7C shows the predicted nucleotide sequence of human GASP1 using an alternative start site. FIG. 7D shows the corresponding predicted amino acid sequence. The follistatin domain is shown in bold and underlined. The end of the sequence is denoted by the asterisk.

FIG. 8A shows the predicted nucleotide sequence to mouse GASP2, while FIG. 8B shows the corresponding predicted amino acid sequence. The follistatin domain is shown in bold and underlined.

FIG. 9A shows the predicted nucleotide sequence to human GASP2, while FIG. 9B shows the corresponding predicted amino acid sequence. The follistatin domain is shown in bold and underlined.

FIG. 10 shows that mouse GASP1 is expressed in many adult tissues and during development. The figure shows tissue expression profiles of mouse GASP1. A 551 bp fragment of GASP1 was amplified from normalized first-strand cDNA panels from Clontech (Palo Alto, Calif.). A portion of glyceraldehyde-3phosphate dehydrogenase (G3PDH) was amplified as a control. G3PDH expression is known to be high in skeletal muscle and low in testis. The cDNA panels were normalized against beta-actin, phospholipase A2, and ribosomal protein S29, in addition to G3PDH.

FIG. 11 shows proteins isolated from human serum. Proteins from a JA16 immunoprecipitate or a control sample (0) were eluted in a mock PBS elution, a competing peptide elution, or a SDS elution. The proteins in the indicated regions of the gel were digested with trypsin and analyzed by LS-MS/MS and database searching. The proteins present in the JA16 sample but not in the control sample were mature GDF-8 (band 16), GDF-8 propeptide and FLRG (band 11), and human GASP1 (band 4). FIG. 11B shows a western blot of an identical JA16 immunoprecipitate probed with an antibody that recognizes mature GDF-8. Bands corresponding to mature and unprocessed GDF-8 isolated from human serum are visible.

FIG. 12 shows representative mass spectra of a peptide derived from GDF-8 and associated proteins isolated from bands 4, 11, and 16 (FIG. 11). The peptide sequence and N-terminal (b ions) and C-terminal (y ions) are shown. A complete listing of identified peptides is provided in Table 1. Spectra are shown from a GASP1 peptide (SEQ ID NO:44) (FIG. 12A), a FLRG peptide (SEQ ID NO:41) (FIG. 12B), a GDF-8 propeptide peptide (SEQ ID NO:24) (FIG. 12C), and a mature GDF-8 peptide (SEQ ID NO:13) (FIG. 12D).

FIG. 13 shows the nucleotide (SEQ ID NO:48) and amino acid (SEQ ID NO:49) sequences of cloned mouse GASP1. The peptides identified by mass spectrometry in JAI 6 affinity-purified samples are underlined. The end of the sequence is denoted by the asterisk.

FIG. 14A shows the domain structure of GASP1. GASP1 has a signal sequence/ cleavage site after amino acid 29. In addition, GASP1 contains two Kunitz/BPTI serine protease inhibitor domains, a follistatin domain (including a Kazal serine protease inhibitor motif) and a netrin domain, which may inhibit metalloproteases.

FIG. 14B shows the phylogenetic tree of GASP1 and GASP2 predicted from the mouse and human genomic sequences. Mouse and human GASP1 are 90% identical. GASP1 and GASP2 are 54% identical.

FIG. 15 shows that recombinantly-produced GASP1 binds separately to both GDF-8 and GDF-8 propeptide. (A) JA16 was used to immunoprecipitate GDF-8 from mock- or GASP1-V5-His transfected COS cell conditioned media supplemented with recombinant purified GDF-8 and/or propeptide. Western blots with anti-V5 (top panel), anti-GDF-8 (middle panel), or anti-propeptide polyclonal antibodies were used to determine whether these proteins were present in the immunoprecipitate. (B) Recombinantly-produced GASP1 protein was immunoprecipitated by anti-V5 tag antibodies from mock- or GASP1-V5-His conditioned media supplemented with recombinant purified GDF-8 and/or propeptide. The immunoprecipitate was analyzed by western blotting as in (A).

FIG. 16 shows that GASP1 inhibits the biological activity of GDF8 and the highly related BMP-11, but not activin or TGF-beta . Various dilutions of conditioned media from mock (open circles) or GASP1-V5-His (filled squares) transfectants were incubated with (A) 10 ng/ml GDF-8, (B) 10 ng/ml BMP-11, (C) 10 ng/ml activin, or (D) 0.5 ng/ml TGF-p. These samples were then subjected to a luciferase reporter activity assay in A204 (A-C) or RD (D) cells to determine the activity of the added growth factors. Luciferase activity is shown in relative luciferase units. The activity resulting from each of the growth factors alone is shown by the filled diamonds and short dashed line. Without addition of any growth factor, the background activity in the assay is low, as shown by the long dashed line with no symbols.

FIG. 17 shows the potency of GASP1 inhibition of GDF-8. Purified GASP1 was tested for its ability to inhibit 20 ng/ml of myostatin in the (CAGA)12 (SEQ ID NO:53) luciferase reporter assay in RD cells (filled squares). The activity resulting from GDF-8 alone is shown by the filled diamonds and short dashed line. The activity present when no growth factors are added is shown by the long dashed line.

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ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Myostatin is a transforming growth factor 13 family member that acts as a negative regulator of skeletal muscle growth. Myostatin circulates in the blood of adult mice in a noncovalently held complex with other proteins, including its propeptide, which maintain the C-terminal dimer in a latent, inactive state. This latent form of myostatin can be activated in vitro by treatment with acid; however, the mechanisms by which latent myostatin is activated in vivo are unknown. Here, we show that members of the bone morphogenetic protein-1/tolloid (BMP-1/TLD) family of metalloproteinases can cleave the myostatin propeptide in this complex and can thereby activate latent myostatin. Furthermore, we show that a mutant form of the propeptide resistant to cleavage by BMP-1/TLD proteinases can cause significant increases in muscle mass when injected into adult mice. These findings raise the possibility that members of the BMP-1/TLD family may be involved in activating latent myostatin in vivo and that molecules capable of inhibiting these proteinases may be effective agents for increasing muscle mass for both human therapeutic and agricultural applications.

=> d his

L1 QUE ((LATENT(W) MYOSTATIN) OR MYOSTATIN OR PROMYOSTATIN)

L2 3032 S L1
L3 119 S (METALLOPROTEASE OR BMP? OR TLD? OR TLL?)(S)L2
L4 63 S (AGENT OR MODULAT? OR INHIBIT? OR ACTIVAT?)(S)L3
L5 23 S CLEAV?(S)L4
L6 13 DUP REM L5 (10 DUPLICATES REMOVED)

=> log y